

PI:	Title: _R03_	
Received:	FOA:	Council: 10/2013
Competition ID:	FOA Title: NIH SMALL RESEARCH GRANT PROGRAM (PARENT R03)	
1 R03	Dual:	Accession Number:
IPF:	Organization:	Department:
Former Number:	Obstetrics and Gynecology	
IRG/SRG: CHHD-A	AIDS: N	Expedited: N
Subtotal Direct Costs (excludes consortium F&A) Year 1: Year 2:	Animals: N Humans: Y Clinical Trial: Y Current HS Code: HESC: N	New Investigator: N Early Stage Investigator: N
<i>Senior/Key</i>	<i>Organization:</i>	<i>Role Category:</i>
<i>Personnel:</i>		PD/PI
		Co-Investigator
		Co-Investigator

APPLICATION FOR FEDERAL ASSISTANCE
SF 424 (R&R)

3. DATE RECEIVED BY STATE

State Application Identifier

1. * TYPE OF SUBMISSION

☐ Pre-application ☒ Application ☐ Changed/Corrected Application

2. DATE SUBMITTED

Applicant Identifier

4. a. Federal Identifier

b. Agency Routing Identifier

5. APPLICANT INFORMATION

* Organizational DUNS:

* Legal Name:

Department:

Division:

* Street1:

Street2:

* City:

County / Parish: orange

* State:

Province:

* Country:

USA: UNITED STATES

* ZIP / Postal Code:

Person to be contacted on matters involving this application

Prefix:

* First Name:

Middle Name:

* Last Name:

Suffix:

* Phone Number:

Fax Number:

Email:

6. * EMPLOYER IDENTIFICATION (EIN) or (TIN):

7. * TYPE OF APPLICANT:

H: Public/State Controlled Institution of Higher Education

Other (Specify):

Small Business Organization Type

☐

Women Owned

☐

Socially and Economically Disadvantaged

8. * TYPE OF APPLICATION:

☒ New ☐ Resubmission☐ Renewal ☐ Continuation ☐ Revision

If Revision, mark appropriate box(es).

☐ A. Increase Award☐ B. Decrease Award☐ C. Increase Duration☐ D. Decrease Duration☐ E. Other (specify):* Is this application being submitted to other agencies? Yes ☐ No ☒

What other Agencies?

9. * NAME OF FEDERAL AGENCY:

National Institutes of Health

10. CATALOG OF FEDERAL DOMESTIC ASSISTANCE NUMBER:

TITLE:

11. * DESCRIPTIVE TITLE OF APPLICANT'S PROJECT:

12. PROPOSED PROJECT:

* Start Date

* Ending Date

* 13. CONGRESSIONAL DISTRICT OF APPLICANT

14. PROJECT DIRECTOR/PRINCIPAL INVESTIGATOR CONTACT INFORMATION

Prefix:

* First Name:

Middle Name:

* Last Name:

Suffix:

Position/Title:

Assoc Prof

* Organization Name:

Department:

Obstetrics and Gynecology

Division:

* Street1:

Street2:

* City:

County / Parish:

* State:

Province:

* Country:

USA: UNITED STATES

* ZIP / Postal Code:

* Phone Number:

Fax Number:

* Email:

15. ESTIMATED PROJECT FUNDING a. Total Federal Funds Requested <input style="width: 150px;" type="text"/> b. Total Non-Federal Funds <input style="width: 150px;" type="text" value="0.00"/> c. Total Federal & Non-Federal Funds <input style="width: 150px;" type="text"/> d. Estimated Program Income <input style="width: 150px;" type="text" value="0.00"/>	16. * IS APPLICATION SUBJECT TO REVIEW BY STATE EXECUTIVE ORDER 12372 PROCESS? a. YES <input type="checkbox"/> THIS PREAPPLICATION/APPLICATION WAS MADE AVAILABLE TO THE STATE EXECUTIVE ORDER 12372 PROCESS FOR REVIEW ON: DATE: <input style="width: 100px;" type="text"/> b. NO <input checked="" type="checkbox"/> PROGRAM IS NOT COVERED BY E.O. 12372; OR <input type="checkbox"/> PROGRAM HAS NOT BEEN SELECTED BY STATE FOR REVIEW
17. By signing this application, I certify (1) to the statements contained in the list of certifications* and (2) that the statements herein are true, complete and accurate to the best of my knowledge. I also provide the required assurances * and agree to comply with any resulting terms if I accept an award. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. (U.S. Code, Title 18, Section 1001) <input checked="" type="checkbox"/> * I agree <small>* The list of certifications and assurances, or an Internet site where you may obtain this list, is contained in the announcement or agency specific instructions.</small>	
18. SFLLL or other Explanatory Documentation <div style="border: 1px solid black; height: 20px; width: 450px; margin-bottom: 5px;"></div> <div style="display: flex; justify-content: flex-end; gap: 10px;"><div style="border: 1px solid black; padding: 2px 10px; background-color: #f0f0f0;">Add Attachment</div><div style="border: 1px solid black; padding: 2px 10px; background-color: #f0f0f0;">Delete Attachment</div><div style="border: 1px solid black; padding: 2px 10px; background-color: #f0f0f0;">View Attachment</div></div>	
19. Authorized Representative <div style="display: flex; justify-content: space-between; margin-bottom: 5px;"><div>Prefix: <input style="width: 80px;" type="text" value="Dr."/></div><div>* First Name: <input style="width: 250px;" type="text"/></div><div>Middle Name: <input style="width: 180px;" type="text"/></div></div> <div style="display: flex; justify-content: space-between; margin-bottom: 5px;"><div>* Last Name: <input style="width: 450px;" type="text"/></div><div>Suffix: <input style="width: 100px;" type="text" value="Ph.D."/></div></div> <div style="margin-bottom: 5px;">* Position/Title: <input style="width: 350px;" type="text" value="Vice Chancellor for Research"/></div> <div style="margin-bottom: 5px;">* Organization: <input style="width: 450px;" type="text"/></div> <div style="display: flex; justify-content: space-between; margin-bottom: 5px;"><div>Department: <input style="width: 200px;" type="text" value="Office of Sponsored Research"/></div><div>Division: <input style="width: 200px;" type="text" value="Research"/></div></div> <div style="margin-bottom: 5px;">* Street1: <input style="width: 400px;" type="text"/></div> <div style="margin-bottom: 5px;">Street2: <input style="width: 400px;" type="text"/></div> <div style="display: flex; justify-content: space-between; margin-bottom: 5px;"><div>* City: <input style="width: 250px;" type="text"/></div><div>County / Parish: <input style="width: 200px;" type="text"/></div></div> <div style="display: flex; justify-content: space-between; margin-bottom: 5px;"><div>* State: <input style="width: 400px;" type="text"/></div><div>Province: <input style="width: 150px;" type="text"/></div></div> <div style="display: flex; justify-content: space-between; margin-bottom: 5px;"><div>* Country: <input style="width: 400px;" type="text" value="USA: UNITED STATES"/></div><div>* ZIP / Postal Code: <input style="width: 150px;" type="text"/></div></div> <div style="display: flex; justify-content: space-between; margin-bottom: 5px;"><div>* Phone Number: <input style="width: 150px;" type="text"/></div><div>Fax Number: <input style="width: 150px;" type="text"/></div></div> <div style="margin-bottom: 5px;">* Email: <input style="width: 450px;" type="text"/></div> <div style="display: flex; justify-content: space-between; margin-top: 20px;"><div style="width: 45%; text-align: center;">* Signature of Authorized Representative <div style="border: 1px solid black; height: 20px; width: 100%; margin-top: 5px;"></div></div><div style="width: 45%; text-align: center;">* Date Signed <div style="border: 1px solid black; height: 20px; width: 100%; margin-top: 5px;"></div></div></div>	
20. Pre-application <input style="width: 300px;" type="text"/> <div style="display: flex; justify-content: flex-end; gap: 10px; margin-top: 5px;"><div style="border: 1px solid black; padding: 2px 10px; background-color: #f0f0f0;">Add Attachment</div><div style="border: 1px solid black; padding: 2px 10px; background-color: #f0f0f0;">Delete Attachment</div><div style="border: 1px solid black; padding: 2px 10px; background-color: #f0f0f0;">View Attachment</div></div>	

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Project/Performance Site Location(s)**Project/Performance Site Primary Location**☐ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.Organization Name: DUNS Number: * Street1: Street2: * City: County: * State: Province:

* Country: USA: UNITED STATES

* ZIP / Postal Code: * Project/ Performance Site Congressional District: **Project/Performance Site Location 1**☐ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.Organization Name: DUNS Number: * Street1: Street2: * City: County: * State: Province:

* Country: USA: UNITED STATES

* ZIP / Postal Code: * Project/ Performance Site Congressional District: **Additional Location(s)**

Add Attachment

Delete Attachment

View Attachment

RESEARCH & RELATED Other Project Information1. * Are Human Subjects Involved? ☒ Yes ☐ No

1.a If YES to Human Subjects

Is the Project Exempt from Federal regulations? ☐ Yes ☒ NoIf yes, check appropriate exemption number. ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6If no, is the IRB review Pending? ☒ Yes ☐ NoIRB Approval Date: Human Subject Assurance Number: 2. * Are Vertebrate Animals Used? ☐ Yes ☒ No

2.a. If YES to Vertebrate Animals

Is the IACUC review Pending? ☐ Yes ☐ NoIACUC Approval Date: Animal Welfare Assurance Number 3. * Is proprietary/privileged information included in the application? ☒ Yes ☐ No4.a. * Does this project have an actual or potential impact on the environment? ☐ Yes ☒ No4.b. If yes, please explain: 4.c. If this project has an actual or potential impact on the environment, has an exemption been authorized or an environmental assessment (EA) or environmental impact statement (EIS) been performed? ☐ Yes ☐ No4.d. If yes, please explain: 5. * Is the research performance site designated, or eligible to be designated, as a historic place? ☐ Yes ☒ No5.a. If yes, please explain: 6. * Does this project involve activities outside of the United States or partnerships with international collaborators? ☐ Yes ☒ No6.a. If yes, identify countries: 6.b. Optional Explanation: 7. * Project Summary/Abstract 8. * Project Narrative 9. Bibliography & References Cited 10. Facilities & Other Resources 11. Equipment 12. Other Attachments ☐

Project Summary/Abstract and Relevance

Gestational diabetes (GDM) complicates ~500,000 pregnancies annually resulting in significant maternal and fetal morbidity. Recurrent GDM is common and perpetuates a cycle of risk for unhealthy weight and metabolic disease in mother and her future children. Our current macronutrient recommendations and dietary strategies for pregnant women have failed to reduce maternal obesity, prevalence of GDM, or the risk for recurrent GDM. Several appetite signaling hormones and peptides such as ghrelin, peptide YY (PYY), and glucagon-like peptide 1 (GLP-1) are involved in insulin sensitivity and secretion, weight control and fat deposition, and they may be important in the pathogenesis of GDM, the maintenance of postpartum excess weight, and the recurrence of GDM. We will prospectively enroll 30 obese pregnant women (15 with a prior history of medically treated GDM and 15 with no prior history) in a randomized cross-over study to accomplish the following **specific aims**: **1)** To measure fasting and postprandial appetite signaling hormone and gut peptide levels among women with and without prior history of GDM; **2)** To quantify maternal appetite signaling hormone and gut peptide responses following a routine macronutrient low-glycemic meal vs. a higher protein low-glycemic meal; **3)** To measure associations between appetite signaling hormone and gut peptide responses following a routine macronutrient low-glycemic meal versus higher protein low-glycemic meal and pregnancy outcomes (maternal GWG, infant birthweight, presence of GDM). **Our translational research proposal builds upon animal and human data on appetite signaling hormone and gut peptide responses to generate formative data for an application for extramural funding to conduct a randomized clinical trial of innovative dietary strategies to reduce GDM.**

Narrative

Gestational diabetes (GDM) complicates ~500,000 pregnancies annually resulting in significant maternal and fetal morbidity. Recurrent GDM is common and perpetuates a cycle of risk for unhealthy weight and metabolic disease in mother and her future children. Our current macronutrient recommendations and dietary strategies for pregnant women have failed to reduce maternal obesity, prevalence of GDM, or the risk for recurrent GDM. Our translational research proposal builds upon animal and human data on appetite signaling hormone and gut peptide responses to generate formative data for an application for extramural funding to conduct a randomized clinical trial of innovative dietary strategies to reduce GDM.

RESOURCES/FACILITIES

Research Environment

_____ has a strong presence nationally in the medical/academic research community as reflected in a number of national rankings for research universities in the U.S. _____ ranks among the top U.S. public universities in research support. Faculty attracted more than \$803 million in total contract and grant funding in fiscal 2010 – up 12.2percent over the previous year and double the amount awarded a decade ago. This year's figure includes a strong showing (\$171 million) in the level of federal stimulus research funding awarded as part of the American Recovery and Reinvestment Act. With its steady growth over the past _____, research funding has become the University's largest revenue stream (_____) – a great tribute to the success of the faculty and a multidisciplinary approach to advancing knowledge and science.

In _____, the University was awarded a prestigious **Clinical and Translational Science Award (CTSA)** – This is accomplished by reducing the time it takes for laboratory discoveries to become treatments for patients, engaging communities with clinical research efforts, and training a new generation of clinical and translational researchers. These tasks are managed by the _____ Translational and Clinical Sciences Institute (_____) which is detailed further in this proposal.

Libraries

_____ academic and research communities benefit from a library with 6.7 million volumes and 80,000 serial titles that perennially ranks among the best research libraries in North America as judged by the **Association of Research Libraries**. The most recent association listings place _____ 15th among 115 research libraries in North America. _____ Southern Historical Collection, with more than 24 million unique items, is the largest collection anywhere of materials that document the region.

A network of libraries and reading rooms across the campus supports the academic, research, and professional programs. More than 300 library staff members provide library services to _____ students, faculty, and staff as well as researchers from throughout _____ and across the globe. The University libraries combined holdings exceed 5 million volumes; 4 million microforms; nearly 2 million government publications; 20 million manuscripts; hundreds of thousands of audiovisuals, maps and photographs; and thousands of electronic titles. In terms of subject scope, campus libraries cover most areas of the fine arts, biomedical and physical sciences, humanities, law, and social sciences.

The University Library,

_____, a special collections facility that includes the Manuscripts, Maps, and Rare Book collections, the _____ Collection and gallery; and nearly a dozen branch libraries covering art, biology, chemistry, geological sciences, information and library science, math/physics, marine sciences, music, and city and regional planning.

University IT infrastructure

The Office of Information Technology Services major computing equipment is available to researchers through the University's central services. These include: a large multi-processor workstation cluster running the Unix operating system with access to terabytes of storage; a robotic tape cartridge system with multiple drives used by a variety of centrally-provided machines for backup and archival; an IBM 3090 computer running MVS/ESA with JES2 and VM/CMS both under VM/XA (a large water-cooled mainframe with a vector (supercomputer) facility); 52 IBM 3380-type disk drives (at least 80 billion bytes); 1 STK 4400 automated cartridge system that is a robotic retrieval system capable of storing 6,000 high-density tapes and delivering them to users within 30 seconds; several local 3174/3274 controllers; 9 STC 3670 tape drives (6250bpi); computer tape backup in separate buildings. Also, has 10 megabit per second switched ethernet to the desktop, 100 megabit connections to all campus buildings, and gigabit connections to the larger Internet as an early adopter of Internet II. T

The Supercomputer Center has a Cray Y-MP/432 with associated equipment. All servers on the system are firewalled at the campus perimeter with data backed up nightly. Physical access to the equipment is tightly controlled; end user access is controlled by a centrally-managed directory service, and is password protected.

Computer Software

An extensive library of software is available on the campus via site licenses or volume purchase agreements. The collection includes all the common statistical analysis languages and packages (SAS, S-Plus, SPSS-X, BMDP, SUDAAN, etc.); development languages (C++, C, Java, PL/1, Fortran, etc.) Packages such as SAS are available on multiple platforms. An analysis can scale from the smaller capacities of a personal computer, then on to the larger capacities of a departmental Unix workstation and finally to the multiple-processor workstations and clusters provided centrally by the campus information technology organization.

THE HEALTH AFFAIRS CAMPUS

Unlike many universities in which the medical center is located miles from the main campus, the Academic Affairs campus and the Health Affairs campus are contiguous. This proximity fosters ongoing collaboration between faculty investigators from a wide variety of disciplines, as noted in this application. Among the disciplines under the Academic Affairs division, a number of departments have high national rankings.

also has an exceptionally strong postdoctoral training program, with more than postdoctoral fellows continuing their research training on the campus. According to the most current data available, is ninth in public universities in terms of numbers of postdoctoral fellows, who have been attracted to because of its research strength.

The School of Medicine

The School of Medicine was formally established in , but there is evidence that medical instruction was given in prior to the Civil War. At the time, there were three faculty members and a total of 37 individuals who had attended this early School of Medicine.

Today the School of Medicine is home to full-time and part-time faculty members. There are departments and centers/programs with entering MD students each year with a total enrollment of . currently has an integrated health care system t

Care; both organizations are committed to service in education, research and patient care to serve the people of _____ and beyond.

Department of Obstetrics and Gynecology/School of Medicine

The Department of Obstetrics and Gynecology has six divisions, representing all of the board certified subspecialties of ObGyn. The divisions are Advanced Laparoscopy and Pelvic Pain, Gynecologic Oncology, Maternal Fetal Medicine, Reproductive Endocrinology and Infertility, Urogynecology and Reconstructive Pelvic Surgery, and Women's Primary Healthcare. The department currently has over _____ faculty members conducting clinical research, with _____ clinical trials undertaken in the last three years within the department. All computers are connected via the local area network to the University mainframe computers. **Dr. _____, the PI of this proposal, is a Professor in the Division of Maternal Fetal Medicine within the Department of Obstetrics and Gynecology.**

_____ In addition the division has a conference room within its space equipped with a state of the art LCD projector and high definition monitor.

_____. The opening of the Women's Hospital means all offices described in this section are within easy walking distance _____ of each other. In addition, _____ has access to offices, conference room space, and teleconferencing capabilities at the Center for Women's Health Research, which is described in a preceeding section of this proposal.

Computers - Department of Obstetrics and Gynecology

The Department maintains personal computers with Intel dual core processors and a minimum of 2.99 GB RAM. These computers are used by the physicians and support personnel. Each is connected to their respective departmental and _____ networks. Each clinic exam room, consultation room, and operative suite within the _____ Women's Hospital has a personal computer that is dedicated exclusively for record-keeping. These computers are linked to the Clinical Work Station of the _____ Hospitals, making hospital census, laboratory results, operative and radiology reports, discharge summaries, and clinic notes available online.

Each personal computer is linked to a sophisticated information technology system maintained by the _____. Fiber optic cable allows high-speed access to the Internet and the Computing Center. This centralized computer facility consists of a SUN ES-1000 with 32 400 MHz processors and 16 GB of main memory. Internally, the department possesses an impressive inventory of computing power configured to accommodate the most demanding of research designs. All computers are networked to Novell and Linux file servers, an arrangement that allows users to exchange files and to print to networked peripheral devices. The servers also function as repositories for shared applications and administrative and project-related information. The department maintains a full complement of sophisticated current software applications that are used for statistical analysis, project management, graphics, web publishing, data management, and databases.

Offices—Department of Obstetrics and Gynecology

The Department is housed in a spacious office suite _____

_____ This location maximizes critical linkages between the division, hospitals, and university. Each division, department, and center utilizes its own office space on the campus of _____, all of which are located a short walking distance or campus bus ride from one another. The office resources include communications using state-of-the-art equipment with the _____ Information Technology Services and an intranet of micro-computers used for word and data processing, presentation development, and desktop publishing. There is immediate, 24-hour electronic communication with co-workers located throughout the world via its Internet video conferencing. In addition, laboratory space is available to each establishment conducting clinical research. Lastly, office support staff and materials are available for use.

Subjects for this proposal will be recruited from the _____ Women's Clinic and Hospital. The Women's Hospital opened in _____, bringing into a single structure nearly all resources dedicated to the provision of health care services for women. The facility includes Women's Outpatient Services, Assisted Reproductive Technology Services, Gynecology Oncology Outpatient Services, Labor & Delivery/Birthing Center with _____ LDRPs and _____ LDRs, an Obstetric Inpatient Unit, a Newborn Nursery with _____

Obstetrical Outpatient Facilities

Obstetrical care is practiced within the _____ Women's Clinic. The Department has _____ over _____ square feet of floor space. There are _____ exam rooms, _____ consultation rooms, and _____ treatment rooms. The Ultrasound Unit is equipped with _____ ultrasound machines including a 360 degree ultrasound. A computerized reporting system and database are integral components of the Ultrasound Unit. All images are captured and stored in digital format. Patients are recruited for clinical studies during their visits _____, and ultrasound, clinical, laboratory data are available through the prenatal record. Study staff have office space allocated in the clinic, which allows for easy access to patients for study recruitment. Offices are locked, and are outfitted with PC desktop computers which are password protected and only accessible by study staff.

LABORATORY FACILITIES

_____ has many state-of-the-art core laboratory facilities available on campus. While each of these core facilities is sponsored by one or more specific units (centers, programs, etc.), there is particular emphasis on the efficiency of shared-use of technical staff, equipment, and facilities. Core labs have combinations of state, federal, and institutional core funding to support such sharing arrangements. They also have a mandate, and in some cases, specific set-asides of funding to assist the career development of new investigators. The core facilities include the following:

_____ The philosophy behind all of the core facilities at _____ is that each facility has its own expert, permanent staff whose job it is to facilitate the use of new technologies by all investigators. This includes both faculty and trainees. Thus the core facilities are particularly effective at introducing investigators to technologies with which they may be unfamiliar.

RELEVANT CENTERS AND PROGRAMS ON THE CAMPUS

_____ was founded _____ as a joint effort of the School of Medicine _____ The mission of the Center is to improve women's health through research by focusing on diseases, disorders and conditions that affect women only, women predominately, and/or women differently than men. Because the field of women's health is extremely broad, the Center has adopted five topical areas to help focus research efforts over the next _____ years:

- Perinatal health
- Cancers affecting women
- Obesity and diabetes
- Women's cardiovascular health
- Women's mental health and substance abuse

As the focal point for women's health research efforts on campus, _____ stimulates scientific endeavors within, among, and across all schools, colleges, centers, and institutes on campus. It is a small organization seeking to identify and link existing efforts in women's health research with related work in other fields, bringing

multiple perspectives to bear on the complex issues inherent in studying and understanding women's health and wellness. Center personnel mine data on current research efforts, identifying gaps and areas of opportunity, discovering new avenues for exploration, mobilizing the research community to develop ways of addressing the gaps and opportunities, and facilitating new areas of research.

. This program emphasizes research related to improving the delivery of health services to women in the state, nation, and throughout the world. As typical of the Center's way of work, their operating principle is to provide connections among research peers, foster career development, infrastructure, and to assure the visibility of women's health research at . As an active member of the will have access to all of the available resources to conduct this research.

has expanded from the and is still one of the very first facilities of its kind, having received its initial funding from the NIH . Now, in grant year , this center represents one of only a handful of that have received continuous support from the NIH since the very inception of the program. The new combines the old and two patient services locations. The location, adjacent to the main hospital, houses clinic facilities: nursing and phlebotomy support and available Monday-Friday 7a.m. to 12 p.m. The Memorial Hospital location provides intensive nursing support and phlebotomy services, 10 outpatient exams rooms and 10 inpatient rooms are available 24 hours a day, seven days a week. This location also offers a Research Subject Advocacy office, a Hispanic Outreach program, and, upon request, offers biostatistical assistance and a bionutrition core. Both facilities are equipped with specimen processing labs and equipment, -80 degree freezers and limited storage areas for study supplies. Center staff assists with the preparation of the IRB application, addendum, sponsor regulatory package, Investigational Drug Service request, budget negotiation, Office of Clinical Trials request form, and internal budget and internal processing forms.

The Memorial Hospital location is a modern, renovated inpatient-outpatient facility that occupies the entire section of Hospital in the very heart of the Medical Center. the Inpatient Facility which includes a spacious, centrally-placed nursing station and private inpatient rooms, each of which is available to investigators on a 24-hours/day, 7 days/week schedule. The north side of the is the Outpatient Facility, which consists of a reception area, a nurses station, an area used for the measurement of height, weight, and vital signs, a phlebotomy/blood processing room, private, fully-equipped examination rooms and consultation room, an IV infusion room, and a waiting/dining room. The inpatient and outpatient rooms are contiguous which allows maximum flexibility in scheduling and staffing.

In addition to the inpatient and outpatient facilities, the houses and staffs a complete research/metabolic kitchen with complete food service capabilities. The research dietitian is a valuable asset to the study team, bringing nutrition knowledge and research expertise to our protocol. The dietitian provides consultation for study design with consideration of research aims, possible confounders, subject burden, food safety, nutrition status, research methodology, grant budgets, and available resources to accomplish your research goals. Throughout the study the research dietitian will work closely with investigators to ensure the integrity of the study. The dietitian's expertise in study implementation and attention to detail at every step is essential to the achievement of our research goals. The research dietitians have unique knowledge and experience in data collection methods and in the analysis of nutrient intake.

In addition to the physical facility, the makes a number of other resources available to all investigators. These resources include:

- A consultation service that includes both a biostatistician and an epidemiologist. Both of these individuals are faculty members in our internationally recognized School of Public Health, and each has regular office hours on the . The biostatistician is Dr. has been instrumental in the development of all of the current awards as well as Dr. K23 award. The epidemiologist is Dr. . In addition, Dr. also serves as the .
- A core research laboratory, which conducts a variety of sophisticated analyses. Of particular note are the catecholamine and β -endorphine determinations, which run on a daily basis for numerous other investigators. In addition, recently expanded their Core Lab to include a mass

spectrometry facility that we were able to obtain with funds from a successful NIH Shared Instrumentation Grant. There is a newly established Body Composition Core Laboratory that includes a metabolic cart and a whole body DEXA scanner.

- A full-time computer systems manager () who has been able to create a local area network. This network makes available to all investigators an extensive array of both hardware and software. Furthermore, through existing high-speed connections within the computer center is easily accessible to investigators from throughout the medical center and campus as well as from more distant sites.
- This office provides on-site oversight of all protocols from the perspective of subject safety. The office provides guidance to investigators in formulating safety-monitoring plans that are now required for all studies, as well as spot audits of the consenting process and investigator records.

The is staffed by a dedicated and thoroughly professional group of individuals, including over research nurses and dietitians. The nurses, the staff of the research kitchen, the informatics core director, the biostatistician, the clinical epidemiologist, and the program directors all work together as a team to ensure that each aspect of clinical investigation-from the design of the study to the conduct of the research, analysis of the data, and reports of the results-is carried out with utmost care and attention to every detail to ensure the safe and effective conduct of all aspects of our human investigation. In addition, the nursing staff does everything possible to make certain that each protocol is conducted in compliance with all aspects of human subjects regulations.

HUMAN SUBJECTS PROTECTIONS

The is responsible for ethical and regulatory oversight of research at that involves human subjects. The administers, supports, and guides the work of the Institutional Review Boards (IRBs) and all related activities. Any research involving human subjects proposed by faculty, staff, or students must be reviewed and approved by an IRB before research may begin, and before related grants may be funded. and the IRBs are critical components of the coordinated , which serves to protect the rights and welfare of human subjects. All components of this program must work together to ensure institutional compliance with ethical principles and regulatory requirements. The following is a mission statement for the coordinated

is committed to expanding and disseminating knowledge for the benefit of the people of and the world. An important part of that commitment to knowledge is research of the highest quality on all aspects of the health and behavior of people, and such research is only possible through the participation of humans as research subjects. Human subjects are partners and participants in research and a precious resource to the university. At , human subjects research is a privilege, but not a right. Consistent with that philosophy, it is the mission of the to ensure that:

1. the rights and welfare of human subjects are paramount in the research process;
2. the highest standards of ethical conduct are employed in all research involving human subjects;
3. research investigators are properly trained in the ethical and regulatory aspects of research with human subjects;
4. research investigators deal honestly and fairly with human subjects, informing them fully of procedures to be followed, and the risks and benefits of participating in research; and
5. research using human subjects at conforms with all applicable local, state, and federal laws and regulations and the policies of the university.

Human Research Ethics Training

Human Research Ethics Training at is governed by the University Policy on Education and Certification of Investigators Involved in Human Subjects Research; this document can be accessed at

The _____ provides a significant number of services to the academic community including:

- Integrated oversight of ethical and regulatory issues in human subjects research conducted at _____; effective and efficient IRB review, expertise of 100 members across seven IRBs, proactive consultation and training
- Development of common tools and resources; standardized application form for all IRBs, standardized consent form templates, _____ web site, standard operating procedures, database for managing and tracking protocols, campus-wide help desk
- Facilitation and strengthening of links to other entities involved in oversight of human research at _____
- Provision of additional resources to improve services and functioning such as compliance and monitoring, training and education, information services and administration
- Achievement of accreditation for _____ through _____

_____ has committed to uphold regulatory and ethical standards through a Federal Wide Assurance approved by the federal _____ and our agreement is _____. _____ and the IRBs are guided by Standard Operating Procedures. An Advisory Committee with broad representation across campus also provides counsel to _____

This _____ committee reviews research involving School of Medicine, School of Pharmacy, _____ Hospitals, and research in other units that involves biomedical interventions. Expertise is focused on medical, surgical, physiological or pharmacological studies and includes research with drugs, devices, counseling, or other interventions. The following is a mission statement for the coordinated Human Research Protection Program:

_____ is committed to expanding and disseminating knowledge for the benefit of the people of _____ and the world. An important part of that commitment to knowledge is research of the highest quality on all aspects of the health and behavior of people, and such research is only possible through the participation of humans as research subjects. Human subjects are partners in research and a precious resource to the university. At _____, human subjects research is a privilege, not a right. Consistent with that philosophy, it is the mission _____ to ensure that:

- The rights and welfare of human subjects are paramount in the research process;
- The highest standards of ethical conduct are employed in all research involving human subjects;
- Research investigators are properly trained in the ethical and regulatory aspects of research with human subjects;
- Research investigators deal honestly and fairly with human subjects, informing them fully of procedures to be followed, and the risks and benefits of participating in research; and
- Research using human subjects at _____ conforms with all applicable local, state, and federal laws and regulations and the policies of the university.

Current IRB structure

Formerly school-based IRB operations have been integrated into a centralized office, reporting through a single director _____. The goal is to maximize protection of human research subjects at _____ through the effective and efficient use of campus resources, increased capacity and accountability and standardization of best practices. Which IRB is used is typically determined by the home department of the principal investigator. The three IRBs at _____ are:

Behavioral IRB reviews research in psychology, child development, education, anthropology, information and library science, social work, journalism, and many other disciplines. Expertise is focused on research in behavioral and social sciences and the humanities.

Biomedical IRB is comprised of four committees: School of Medicine, School of Pharmacy, Hospitals, and Other units that involve biomedical interventions. Expertise is focused on medical, dental, surgical, physiological or pharmacological studies and includes research with drugs, devices, counseling, or other interventions.

Public Health/Nursing IRB reviews research from the School of Public Health, School of Nursing, nursing-related studies at Hospitals, non-medical research from Injury Prevention Research Center, Health Promotion Disease Prevention, and Expertise is focused on behavioral, social, organizational, epidemiological, and other research in a public health or nursing context.

During 2011, the three IRBs reviewed a total of 1,172 studies, 934 that were expedited reviews and 238 that required full Board review. Of the 934 expedited reviews, 168 were approved without changes (median of four days), 534 were approved with one response from the PI (median of 19 days), and 232 required two responses from the PI before approval was granted (median of 30 days). Full Board review typically takes a little longer, but the data remain quite good (Figure 1). Of the 238 studies that went to full Board review, five were approved with no changes (median time four days), 187 were approved with one response from the PI (median time 39 days), and 46 were approved with two responses (median 65 days).

According to a survey among Clinical and Translation Science Award (CTSA) sites in 2009, was ranked ninth of 29 participating sites on number of days to IRB approval. The IRBs continue to focus on improvement, and during the past year have moved to an online submission process. Data for turnaround times since the cutover are not yet available, but the anticipation is that electronic submissions will contribute to the overall positive trend in the improvement of the IRB cycle.

Regulatory documents

The following documents are available through the Office of Human Research Ethics:

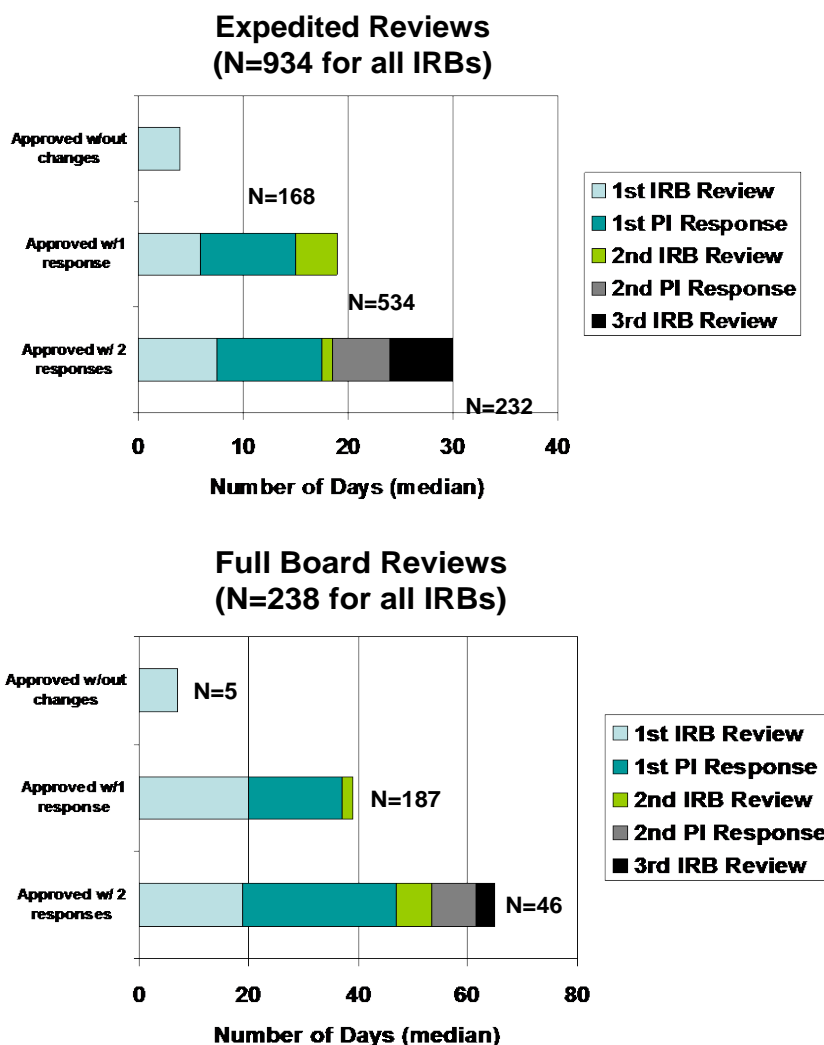
Federal Wide Assurance (FWA)

has committed to uphold regulatory and ethical standards through a Federal Wide Assurance approved by the federal Office for Human Research Protections (OHRP). Our agreement with OHRP is ; the link to this document can be found on the OHRE website at

Statement of Compliance

This document attest that the Institutional Review Boards at the administered by the office of Human Research Ethics, are organized and operate according to applicable laws

Figure 1. IRB Turnaround Times 2011



and regulations governing research involving human subjects. The link to this document can be found on the OHRE website at the above url.

Standard Operating Procedures (SOP)

Human Research Protection Program Standard Operating Procedures describes the policy and procedures that guide the IRBs at our University. This manual is directed to IRB chairs and members, the staff of the Office of Human Research Ethics, and other affiliated persons, and includes policies and procedures applicable to these persons in their capacities with the IRB. The link to SOPs can be found at the OHRE website.

RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Project Director/Principal Investigator			
Prefix:	<input type="text"/>	* First Name:	<input type="text"/>
		Middle Name:	<input type="text"/>
* Last Name:	<input type="text"/>	Suffix:	<input type="text"/>
Position/Title:	<input type="text" value="Assoc Prof"/>	Department:	<input type="text" value="Obstetrics and Gynecology"/>
Organization Name:	<input type="text"/>	Division:	<input type="text"/>
* Street1:	<input type="text"/>		
Street2:	<input type="text"/>		
* City:	<input type="text"/>	County/ Parish:	<input type="text"/>
* State:	<input type="text"/>	Province:	<input type="text"/>
* Country:	<input type="text" value="USA: UNITED STATES"/>	* Zip / Postal Code:	<input type="text"/>
* Phone Number:	<input type="text"/>	Fax Number:	<input type="text"/>
* E-Mail:	<input type="text"/>		
Credential, e.g., agency login:	<input type="text"/>		
* Project Role:	<input type="text" value="PD/PI"/>	Other Project Role Category:	<input type="text"/>
Degree Type:	<input type="text" value="MD"/>		
Degree Year:	<input type="text" value="1990"/>		
*Attach Biographical Sketch	<input type="text"/>	<input type="button" value="Add Attachment"/>	<input type="button" value="Delete Attachment"/>
Attach Current & Pending Support	<input type="text"/>	<input type="button" value="Add Attachment"/>	<input type="button" value="Delete Attachment"/>
		<input type="button" value="View Attachment"/>	<input type="button" value="View Attachment"/>

PROFILE - Senior/Key Person 1			
Prefix:	<input type="text"/>	* First Name:	<input type="text"/>
		Middle Name:	<input type="text"/>
* Last Name:	<input type="text"/>	Suffix:	<input type="text"/>
Position/Title:	<input type="text" value="Adj Asst Prof, Asst Prof"/>	Department:	<input type="text" value="Psychiatry"/>
Organization Name:	<input type="text"/>	Division:	<input type="text"/>
* Street1:	<input type="text"/>		
Street2:	<input type="text"/>		
* City:	<input type="text"/>	County/ Parish:	<input type="text"/>
* State:	<input type="text"/>	Province:	<input type="text"/>
* Country:	<input type="text" value="USA: UNITED STATES"/>	* Zip / Postal Code:	<input type="text"/>
* Phone Number:	<input type="text"/>	Fax Number:	<input type="text"/>
* E-Mail:	<input type="text"/>		
Credential, e.g., agency login:	<input type="text"/>		
* Project Role:	<input type="text" value="Co-Investigator"/>	Other Project Role Category:	<input type="text"/>
Degree Type:	<input type="text" value="PhD"/>		
Degree Year:	<input type="text" value="1996"/>		
*Attach Biographical Sketch	<input type="text"/>	<input type="button" value="Add Attachment"/>	<input type="button" value="Delete Attachment"/>
Attach Current & Pending Support	<input type="text"/>	<input type="button" value="Add Attachment"/>	<input type="button" value="Delete Attachment"/>
		<input type="button" value="View Attachment"/>	<input type="button" value="View Attachment"/>

RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Senior/Key Person 2		
Prefix:	<input type="text"/>	* First Name: <input type="text"/> Middle Name: <input type="text"/>
* Last Name:	<input type="text"/>	Suffix: <input type="text"/>
Position/Title:	<input type="text" value="Adjunct Assistant Professor of Biostatistics"/>	Department: <input type="text"/>
Organization Name:	<input type="text"/>	Division: <input type="text"/>
* Street1:	<input type="text"/>	
Street2:	<input type="text"/>	
* City:	<input type="text"/>	County/ Parish: <input type="text"/>
* State:	<input type="text"/>	Province: <input type="text"/>
* Country:	<input type="text" value="USA: UNITED STATES"/>	* Zip / Postal Code: <input type="text"/>
* Phone Number:	<input type="text"/>	Fax Number: <input type="text"/>
* E-Mail:	<input type="text"/>	
Credential, e.g., agency login: <input type="text"/>		
* Project Role:	<input type="text" value="Co-Investigator"/>	Other Project Role Category: <input type="text"/>
Degree Type:	<input type="text" value="PhD"/>	
Degree Year:	<input type="text" value="2001"/>	
*Attach Biographical Sketch	<input type="text"/>	<input type="button" value="Add Attachment"/> <input type="button" value="Delete Attachment"/> <input type="button" value="View Attachment"/>
Attach Current & Pending Support	<input type="text"/>	<input type="button" value="Add Attachment"/> <input type="button" value="Delete Attachment"/> <input type="button" value="View Attachment"/>

BIOGRAPHICAL SKETCH

NAME	POSITION TITLE		
eRA COMMONS USER NAME	Professor		
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	YEAR(s)	FIELD OF STUDY
	BS MD Residency Fellowship Fellowship Certificate		

A. Personal Statement

I have a broad background in maternal-fetal medicine, with expertise in infection and inflammation in pregnancy and I have just entered the field of diabetes translational research. I have recently begun to investigate the public health implications of identifying and mitigating long-term health risks of obesity and type 2 diabetes among pregnant women. As the alternate PI for the Maternal Fetal Medicine Units (MFMU) Network at _____, I assisted in the execution of the Gestational Diabetes in Pregnancy trial at _____, which demonstrated that treatment of mild forms of glucose intolerance in pregnancy improved perinatal outcomes. I am currently the PI for an MFMU proposal to study the effects of metformin versus insulin for type 2 diabetes in pregnancy. In addition, to complement my expertise I have engaged local experts as co-investigators and created a new multidisciplinary team to share their knowledge for implementation of this proposal and interpretation of findings; the results of this proposal will serve as pilot data and lay the foundation for a future NIH proposal of different dietary strategies to optimize maternal and infant outcomes, reduce morbidity of maternal obesity and excessive GWG, and reduce risk for GDM. Gathering this pilot data is critical to future success as I enter the field of diabetes translational research.

B. Positions and Honors

Positions and Employment

Other Experience and Professional Memberships

Honors

C. Peer-reviewed publications

Most relevant to current application

- 1.
- 2.
- 3.
- 4.
- 5.
- 6.
- 7.

Additional peer-reviewed publications of importance to the field

- 1.
- 2.
- 3.
- 4.
- 5.

6.

7.

D. Research Support

On-going Research Support

1 R01	9/20/	– 7/31/
NIH/NICHD	\$	

The objective of this project is evaluate the comparative effectiveness and safety of azithromycin-based extended-spectrum antibiotic prophylaxis (azithromycin plus standard narrow-spectrum cephalosporin) relative to standard single-agent cephalosporin prior to surgical incision to prevent post-cesarean infection.

No Number	7/1/	– 6/30/
-----------	------	---------

Umbilical cord inflammatory markers in pregnancies complicated by diabetes

The purpose of this study is to measure umbilical cord inflammatory markers in pregnancies complicated by type 2 diabetes.

No Number	2/1/	– 6/30/
-----------	------	---------

Proteomic Assessment of Preterm Birth Risk

The objective of this study is to measure proteomics among a diverse cohort of pregnant women at specific gestational age windows.

No Number	9/1/	– 3/31/
-----------	------	---------

Prenatal Oral Health Program

This project will develop and implement a prenatal oral health education program for prenatal care providers.

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE Assistant Professor of Psychiatry		
eRA COMMONS USER NAME			
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	YEAR(s)	FIELD OF STUDY
	B.S. M.A. Ph.D. Postdoc		

A. Personal Statement

My long-term goals as a clinical intervention scientist are to expand and deepen understanding of the biological determinants of excess obesity risk in ethnic minority women, and to develop and implement individualized behavioral interventions in this high risk group. As co-Investigator, I will lead and direct the dietary challenge and gut peptide aspects of proposed project. While this is a new area of research for the PI, I have nearly 20 years of experience conducting human psychophysiological and intervention research with a focus in women's health, cardiovascular disease, and obesity. Formative NIH-supported work included an F31 () and K23 (). Since 2004 I have been actively researching and publishing in the area of appetite-regulating gut-derived peptides and their role in ethnic disparities in obesity, functional GI disorders (R24 seed grant), and antipsychotic-induced weight gain (R01 , PI). Through these activities I have obtained the requisite knowledge and skills needed to ensure successful completion of the study aims. I was the Principal Investigator on the human feeding, funded through the Clinical and Translational Research Center and the Nutrition Obesity Research Center, which provided preliminary data to support the proposed studies (, et al.,). After successful completion of the proposed research, I will be exceptionally well-positioned and well-equipped to lead the next generation of studies and to expand their translation and application through my on-going collaborations with the Center of Excellence for Eating Disorders, the Stress and Health Research Program, and the Institute on Aging. It is my firm belief that achieving these goals will directly contribute to reducing the individual and societal burdens associated with diabetes and obesity.

B. Positions and Honors

Positions and Employment

Other Experience and Professional Memberships

2002 – 2012

2009 –

2009 –

2010 –

2011 –

2012 –

Honors

1983

1994-1996

2000

2000

2001

2007

2008

C. Selected Peer-reviewed Publications (in reverse chronological order)

has authored or co-authored nearly four dozen papers and chapters – the selection below is most relevant to this application)

1.

2.

3.

4.

5.

6.

7.

8.

9.

10.

11.

12.

13.

14.

15.

D. Research Support

Ongoing Research Support

R01 08/01/ – 05/31/

The goal of this research is to clarify the trajectories and possible outcomes for eating disorder patients, their families, and health care professionals and provide clear targets for treatment studies.
Role: Investigator

Completed Research Support

(PI) 09/25/ – 09/24/

The ultimate goal is to present the “state of the science” on a given topic in a manner that can be directly applied to decisions made by users of health care information. These users include clinicians, patients and caregivers, policy-makers, funders and payers, and may be individuals or their related organizations.
Role: Investigator

R01 (PI) 09/15/ – 04/30/

The goal of this study is to assess prospective changes in postprandial appetite-regulating hormones and metabolism in patients early in treatment with atypical antipsychotic agents.
Role: Principal Investigator

(PI) 07/01/ – 06/30/

This study was a feasibility and preliminary efficacy placebo-controlled, double-blind study of chromium in overweight individuals with binge eating disorder.

11/01/ – 07/31/

(PI)

The goal of this study is to assess the feasibility conducting in-home assessments of CVD biomarkers in caregivers of persons with dementia.
Role: Principal Investigator

R01 07/11/ – 05/01/

The goal of this study is to compare the effects of continuous oral contraceptive treatment vs. placebo on symptoms and neurosteroid responses in women with PMDD.

Role: Co-investigator

(PI) 10/01/ – 09/30/

This study examined gastric emptying rate and appetite hormone dysregulation in patients with postprandial distress syndrome and healthy controls.

Role: Principal Investigator

(PI) 05/01/ – 04/30/

This study evaluated appetite hormone and subjective hunger responses to high versus low glycemic index meals in obese and normal weight African-American and White women.

K23 (PI) 09/15/ – 08/31/

This study examined changes in cardiovascular, neuroendocrine, and metabolic functioning in hypertensive postmenopausal women treated with raloxifene alone versus raloxifene plus exercise for 6 months.

Role: Principal Investigator

F31 (PI) 09/01/ - 01/05/

This study examined sympathetic and adrenergic mechanisms underlying post-exercise hypotension.

Role: Principal Investigator

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE		
eRA COMMONS USER NAME	Research Assistant Professor of Medicine Adjunct Assistant Professor of Biostatistics		
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, and</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	MM/YY	FIELD OF STUDY
	B.S.E.	06/92	Mathematics
	M.S.	05/95	Statistics
	Ph.D.	05/01	Biostatistics

A. Personal Statement

As a faculty biostatistician in the Education, Training, and Career Development Program within the Institute, I provide statistical and study design expertise to clinical and translational research scholars supported by I have more than twelve years' collaborative and consultative experience in non-profit, industry, and academic settings, and have actively contributed to the design, analysis, and interpretation of many randomized, cluster-randomized, and observational studies with clinical, behavioral, and health services research outcomes. My areas of statistical expertise include analysis of longitudinal and survival data, design, analysis, and interpretation of individually- and cluster-randomized trials, and analysis of data from complex sampling designs. I am thus well-suited for my roles in the proposed study, which include assisting with study design (e.g., implementing the randomization plan) and providing oversight and collaborating in the statistical analysis, interpretation, and reporting of the results.

B. Positions and Honors**Positions**

2001-2002
2002-2004
2004-2005
2005-2005
2005-2007
2007-2011
2008-
2011-

Other Experience and Professional Memberships

2005
2006-2007
2008
2011

Honors and Awards

1994
1995
1995-2000

C. Selected peer-reviewed publications

- 1.
- 2.
- 3.
- 4.
- 5.
- 6.
- 7.
- 8.
- 9.
- 10.
- 11.
- 12.
- 13.
- 14.
- 15.

D. Research Support

Ongoing

NIH/NCRR . (PI) 5/20 – 4/20

This is a national consortium grant with the goal of transforming how clinical and translational research is conducted, ultimately enabling researchers to provide new treatments more efficiently and quickly to patients.
Role:

U01 (PI) 10/01/ – 9/30/
CDC

Change in Opioid Use and Overdose After a Medicaid Lock-In Program

To assess the impact of the Management Medicaid Lock-in Program, which was initiated in October of 2010, and to examine changes in controlled substance prescriptions filled among individuals in the , regardless of insurer.

Role:

Completed

N01 . (PI) 9/20 – 8/20
NIH/NIAID

The goal of this project is to enhance the capacity of NIH's Division of Microbiology and Infectious Diseases (DMID) funded international clinical sites to perform clinical research in accordance with international standards.

Role:

GPO (PI) 6/18/20 – 6/17/20

The project seeks to improve access to family planning among underserved populations in developing countries by providing global technical leadership and undertaking concentrated activities in selected countries.

Role:

GHO (PI) 8/17/20 – 8/16/20

The purpose is to support activities related to the development of selected new HIV-preventive technologies and programs that are of strategic interest to USAID and the advancement of its global HIV-prevention and health agenda.

Role: Worked on several projects under this contract.

GPO (PI) 4/29/20 – 4/28/20

The purpose is to support contraceptive research as well as to facilitate its use to improve health programs in developing countries. It includes clinical research, health services research, and behavioral and social sciences research as well as research dissemination and capacity building.

Role: Worked on several projects under this contract. Served as lead statistician, statistical consultant, advisor to junior statisticians and analysts, and statistical trainer (09/20 – 04/20)

Cover Page Supplement

OMB Number:

1. Project Director / Principal Investigator (PD/PI)

Prefix: * First Name:
Middle Name:
* Last Name:
Suffix:

2. Human Subjects

Clinical Trial? ☐ No ☒ Yes
* Agency-Defined Phase III Clinical Trial? ☒ No ☐ Yes

3. Applicant Organization Contact

Person to be contacted on matters involving this application

Prefix: * First Name:
Middle Name:
* Last Name:
Suffix:
* Phone Number: Fax Number:
Email:

* Title:

* Street1:
Street2:
* City:
County/Parish:
* State:
Province:
* Country: * Zip / Postal Code:

Cover Page Supplement

4. Human Embryonic Stem Cells

* Does the proposed project involve human embryonic stem cells?



No



Yes

If the proposed project involves human embryonic stem cells, list below the registration number of the specific cell line(s) from the following list: <http://stemcells.nih.gov/research/registry/>. Or, if a specific stem cell line cannot be referenced at this time, please check the box indicating that one from the registry will be used:

Cell Line(s):



Specific stem cell line cannot be referenced at this time. One from the registry will be used.

Modular Budget

OMB Number:

Budget Period: 1				
Start Date: <input style="width: 100px;" type="text"/>		End Date: <input style="width: 100px;" type="text"/>		
A. Direct Costs			Funds Requested (\$)	
Direct Cost less Consortium F&A			<input style="width: 100px;" type="text" value="50000"/>	
Consortium F&A			<input style="width: 100px;" type="text"/>	
Total Direct Costs			<input style="width: 100px;" type="text" value="50,000.00"/>	
B. Indirect Costs				
	Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base (\$)	Funds Requested (\$)
1.	<input style="width: 95%;" type="text" value="Organized Research_On Campus"/>	<input style="width: 50px;" type="text" value="52.00"/>	<input style="width: 100px;" type="text" value="50,000.00"/>	<input style="width: 100px;" type="text" value="26,000.00"/>
2.	<input style="width: 95%;" type="text"/>	<input style="width: 50px;" type="text"/>	<input style="width: 100px;" type="text"/>	<input style="width: 100px;" type="text"/>
3.	<input style="width: 95%;" type="text"/>	<input style="width: 50px;" type="text"/>	<input style="width: 100px;" type="text"/>	<input style="width: 100px;" type="text"/>
4.	<input style="width: 95%;" type="text"/>	<input style="width: 50px;" type="text"/>	<input style="width: 100px;" type="text"/>	<input style="width: 100px;" type="text"/>
Cognizant Agency (Agency Name, POC Name and Phone Number)		<input style="width: 95%;" type="text"/>		
Indirect Cost Rate Agreement Date <input style="width: 100px;" type="text"/>			Total Indirect Costs	<input style="width: 100px;" type="text" value="26,000.00"/>
C. Total Direct and Indirect Costs (A + B)			Funds Requested (\$)	<input style="width: 100px;" type="text" value="76,000.00"/>

Budget Period: 2				
Start Date: <input style="width: 100px;" type="text" value="09/01/2014"/>		End Date: <input style="width: 100px;" type="text" value="08/31/2015"/>		
A. Direct Costs			Funds Requested (\$)	
Direct Cost less Consortium F&A			<input style="width: 100px;" type="text" value="50000"/>	
Consortium F&A			<input style="width: 100px;" type="text"/>	
Total Direct Costs			<input style="width: 100px;" type="text" value="50,000.00"/>	
B. Indirect Costs				
	Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base (\$)	Funds Requested (\$)
1.	<input style="width: 95%;" type="text" value="Organized Research_On Campus"/>	<input style="width: 50px;" type="text" value="52.00"/>	<input style="width: 100px;" type="text" value="50,000.00"/>	<input style="width: 100px;" type="text" value="26,000.00"/>
2.	<input style="width: 95%;" type="text"/>	<input style="width: 50px;" type="text"/>	<input style="width: 100px;" type="text"/>	<input style="width: 100px;" type="text"/>
3.	<input style="width: 95%;" type="text"/>	<input style="width: 50px;" type="text"/>	<input style="width: 100px;" type="text"/>	<input style="width: 100px;" type="text"/>
4.	<input style="width: 95%;" type="text"/>	<input style="width: 50px;" type="text"/>	<input style="width: 100px;" type="text"/>	<input style="width: 100px;" type="text"/>
Cognizant Agency (Agency Name, POC Name and Phone Number)		<input style="width: 95%;" type="text"/>		
Indirect Cost Rate Agreement Date <input style="width: 100px;" type="text"/>			Total Indirect Costs	<input style="width: 100px;" type="text" value="26,000.00"/>
C. Total Direct and Indirect Costs (A + B)			Funds Requested (\$)	<input style="width: 100px;" type="text" value="76,000.00"/>




Modular Budget

Cumulative Budget Information

1. Total Costs, Entire Project Period

Section A, Total Direct Cost less Consortium F&A for Entire Project Period	\$	<input type="text" value="100,000.00"/>
Section A, Total Consortium F&A for Entire Project Period	\$	<input type="text"/>
Section A, Total Direct Costs for Entire Project Period	\$	<input type="text" value="100,000.00"/>
Section B, Total Indirect Costs for Entire Project Period	\$	<input type="text" value="52,000.00"/>
Section C, Total Direct and Indirect Costs (A+B) for Entire Project Period	\$	<input type="text" value="152,000.00"/>

2. Budget Justifications

	Personnel Justification	<input type="text"/>	<input type="button" value="Add Attachment"/>	<input type="button" value="Delete Attachment"/>	<input type="button" value="View Attachment"/>
	Consortium Justification	<input type="text"/>	<input type="button" value="Add Attachment"/>	<input type="button" value="Delete Attachment"/>	<input type="button" value="View Attachment"/>
	Additional Narrative Justification	<input type="text"/>	<input type="button" value="Add Attachment"/>	<input type="button" value="Delete Attachment"/>	<input type="button" value="View Attachment"/>

BUDGET JUSTIFICATION

Personnel

Principal Investigator (0.4 calendar months years 1 and 2) is Professor of Maternal Fetal Medicine in the Department of Obstetrics and Gynecology, and Program Director

completed residency at the , followed by an NIAID-funded Infectious Diseases fellowship. completed her Maternal Fetal Medicine fellowship at and is a board certified Maternal Fetal Medicine specialist. She also has received a Certificate in Health Disparities Research. Her research emphasizes infection-related complications of pregnancy and has made significant contributions to understanding the role of infection and inflammation in adverse pregnancy outcomes, including diagnosis and management of diabetes in pregnancy.

has experience with working with large teams and coordinating clinical trials; she currently is the PI for a proposal to be executed by the MFMU Network examining the effects of metformin versus insulin for the treatment of type-2 diabetes in pregnancy. is entering the field of translational diabetes research; the results from this proposal will serve as the foundation for a larger clinical trial of innovative dietary strategies to reduce the risk of gestational diabetes. is responsible for assembling the **multidisciplinary study team** for the current proposal. Creation of this study team is integral to the conduct of the research; each member adds valuable expertise to complement the other investigators as outlined below.

as PI of this proposal, will be responsible for the oversight, administration, and organization of the study protocol. She will supervise the Project Manager, as well as coordinate the array of activities required for this proposal, including subject recruitment, data management, quality assurance checks, data collection, and analysis. She will also personally orient all key personnel to the details of the study and be responsible for communication among investigators. will chair study team meetings: monthly with the Project Manager and quarterly with the co-Investigators, to ensure that study tasks are being completed and all members of the team can provide input and guidance regarding execution of the protocol. At completion of the study, will coordinate writing the final report, manuscripts, and developing follow-up research, including the planned NIH grant.

co-Investigator (0.4 calendar months years 1 and 2) is an investigator in the Department of Psychiatry and a principal faculty member of the Research Program and the . She brings to the study team expertise in psychobiology of appetite regulation including the study of hormones that signal hunger and satiety, how such hormones respond to different types of food, and the role that these hormones play in weight gain.

assisted with study design, and will provide guidance regarding specimen collection and processing, data collection and analysis.

co-Investigator (0.5 calendar months years 1 and 2) is a Research Assistant Professor in the Department of Biostatistics and Department of Medicine in the School of Medicine. As a faculty biostatistician in the Education, Training, and Career Development Program within the provided study design expertise for development of this proposal. He will use his areas of statistical expertise to assist with analysis and interpretation data obtained.

Project Manager (0.7 calendar months years 1 and 2) is Director of Perinatal Research at t , and chairperson of the Perinatal Research Advisory Board. is a Certified Clinical Research Coordinator and is responsible for coordinating perinatal research under the direction of the Perinatal Research Advisory Board. She has more than 25 years experience as a research nurse. She will serve as the Project Coordinator, including screening charts, approaching eligible women, enrolling subjects, and scheduling CTSC visits. These efforts will be accomplished within the

established infrastructure of the Perinatal Research group, which employs 2 full time research assistants who are supervised by .

CTRC Research Technician, (0.6 calendar months years 1 and 2), will process blood specimens. Specimens need to be processed and frozen immediately to ensure integrity of the assays.

, **CTRC Research Technician**, (0.2 calendar months years 1 and 2) will perform all assays.

Research Plan

1. Application Type:

From (R&R) Cover Page. The response provided on that page, regarding the type of application being submitted, is repeated for your reference, as you attach the appropriate sections of the Research Plan.

*Type of Application:

☒ New ☐ Resubmission ☐ Renewal ☐ Continuation ☐ Revision

2. Research Plan Attachments:

Please attach applicable sections of the research plan, below.

1. Introduction to Application (for RESUBMISSION or REVISION only)	<input type="text"/>	Add Attachment	Delete Attachment	View Attachment
2. Specific Aims	<input type="text"/>	Add Attachment	Delete Attachment	View Attachment
3. *Research Strategy	<input type="text"/>	Add Attachment	Delete Attachment	View Attachment
4. Inclusion Enrollment Report	<input type="text"/>	Add Attachment	Delete Attachment	View Attachment
5. Progress Report Publication List	<input type="text"/>	Add Attachment	Delete Attachment	View Attachment

Human Subjects Sections

6. Protection of Human Subjects	<input type="text"/>	Add Attachment	Delete Attachment	View Attachment
7. Inclusion of Women and Minorities	<input type="text"/>	Add Attachment	Delete Attachment	View Attachment
8. Targeted/Planned Enrollment Table	<input type="text"/>	Add Attachment	Delete Attachment	View Attachment
9. Inclusion of Children	<input type="text"/>	Add Attachment	Delete Attachment	View Attachment

Other Research Plan Sections

10. Vertebrate Animals	<input type="text"/>	Add Attachment	Delete Attachment	View Attachment
11. Select Agent Research	<input type="text"/>	Add Attachment	Delete Attachment	View Attachment
12. Multiple PD/PI Leadership Plan	<input type="text"/>	Add Attachment	Delete Attachment	View Attachment
13. Consortium/Contractual Arrangements	<input type="text"/>	Add Attachment	Delete Attachment	View Attachment
14. Letters of Support	<input type="text"/>	Add Attachment	Delete Attachment	View Attachment
15. Resource Sharing Plan(s)	<input type="text"/>	Add Attachment	Delete Attachment	View Attachment

16. Appendix	Add Attachments	Remove Attachments	View Attachments
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SPECIFIC AIMS

Gestational diabetes (GDM) complicates ~480,000 pregnancies annually. The prevalence of GDM is increasing at an alarming rate with the largest relative increase occurring among African-American women. Infants of women with GDM are at risk for in-utero overgrowth (macrosomia and large-for-gestational age) and birth trauma. Maternal risk persists after delivery and future children are also at risk because GDM recurs for half of women with a history in a prior pregnancy. Strategies to reduce recurrent maternal GDM may thus mitigate maternal health risks as well as lessen the intergenerational health effects of GDM for the fetus.

Current strategies to prevent GDM include promotion of healthy maternal weight with lactation, dietary counseling, and exercise. Sadly, these strategies are ineffective, as 30-50% of pregnant women either begin pregnancy overweight/obese or have excessive gestational weight gain (GWG) during pregnancy. Understanding why current lifestyle strategies fail to promote healthy weight or desired GWG is necessary to reduce GDM risk among high-risk women. **Our proposal is the first step to address this gap in our knowledge by quantifying fasting and postprandial appetite signaling hormone and gut satiety peptide responses among pregnant women with a prior history of GDM.**

The appetite-signaling hormone, ghrelin, and satiety peptides such as peptide YY (PYY) and glucagon-like peptide 1 (GLP-1) are involved in insulin sensitivity and secretion, weight control, and fat deposition. Our work has shown unique patterns of postprandial ghrelin and PYY release in non-pregnant women who differ in their overall obesity risk. Limited data suggest that increased ghrelin and blunted PYY and GLP-1 are associated with GDM, with most studies examining only the fasted state. In pregnant non-obese women, GLP-1 level is negatively associated with maternal GWG, and GLP-1 secretion is blunted following a glucose load among women who develop GDM. Taken together, these data suggest that appetite signaling hormones and gut satiety peptides may be important in the pathogenesis of GDM. However, there is a specific need to understand appetite-signaling hormone and gut satiety peptide responses to whole meal challenges in women with GDM, because ghrelin, PYY, and GLP-1 are differentially sensitive to macronutrient manipulation. This information would stimulate development of new dietary recommendations and individualized dietary plans for healthy pregnancy weight management and reduce GDM risk. **Our proposal builds upon animal and human data to generate data for an application for extramural funding to conduct a randomized trial of innovative dietary strategies to reduce GDM recurrence risk.**

Our **long-range goal** is to reduce the adverse effects of GDM and obesity for both mother and child. As a first step, the **primary objective of this proposal** is to quantify maternal appetite signaling hormone and gut satiety peptide levels following mixed macronutrient meals among pregnant women at 20-22 weeks' gestation. We will prospectively enroll 30 pregnant women (15 with a prior history of medically treated GDM and 15 with no prior history) in a randomized cross-over study of two meals that differ in macronutrient composition to accomplish the following **specific aims**: **1)** To measure appetite signaling hormone and gut satiety peptide levels following mixed macronutrient meals among women with and without prior history of GDM; **2)** To quantify maternal appetite signaling hormone and gut satiety peptide responses following a routine low-glycemic meal vs. a higher protein low-glycemic meal; **3)** To measure association between fasting and postprandial appetite signaling hormone and gut satiety peptide responses and pregnancy outcomes (maternal GWG, infant birthweight, presence of GDM). We intend to demonstrate that women with prior GDM have higher postprandial appetite signaling hormone (ghrelin) and lower gut satiety peptide (PYY and GLP-1) responses than women without a history of GDM, and that a meal with higher protein results in lower ghrelin and higher PYY and GLP-1 than a routine macronutrient meal. The **hypotheses to be tested** are **1)** Women with previous GDM have a lower postprandial PYY response compared with women with no history of GDM; **2)** PYY responses are higher following a higher protein meal than following a routine meal among women with and without prior GDM history; and **3)** PYY responses are negatively correlated with maternal GWG. The results generated by this proposal will increase knowledge of biologic mechanisms of appetite control and weight gain to inform potential dietary intervention strategies to reduce GDM.

In summary, GDM is a major public health problem with increasing prevalence that can adversely impact long term maternal and infant health. Unfortunately, there are no current proven strategies to reduce GDM risk among high-risk women. We believe an innovative approach to dietary management is needed to address the gaps in our knowledge. The results generated by this proposal will address these gaps so that dietary interventions can be tailored to promote healthy GWG and glucose homeostasis. We have assembled a multidisciplinary team with expertise in GDM, clinical trials, appetite regulation and obesity, and biostatistics and are leveraging existing infrastructure to ensure successful completion of this proposal. Our results will serve as formative data for an application for extramural funding of dietary interventions to reduce GDM risk and excessive GWG among high-risk women.

RESEARCH STRATEGY SIGNIFICANCE

Gestational diabetes is a growing public health problem

GDM affects 5-12% of all pregnancies, thus up to 480,000 mothers and infants are affected annually in the United States. The rate of GDM has been rising steadily since the 1990s (**Figure 1**). GDM is associated with significant maternal and infant morbidity including preeclampsia, fetal overgrowth [macrosomia, large-for-gestational age (LGA)], fetal organomegaly (hepatomegaly, cardiomegaly), birth trauma, perinatal mortality, and neonatal respiratory and metabolic complications (hypoglycemia, hyperbilirubinemia).² GDM accounts for the largest proportion of maternal delivery hospitalizations complicated by diabetes: 85% compared to 7% for type 1 DM and 5% for type 2 DM.³ The annual health care costs for U.S. women and children that are attributable to GDM are approximately **\$635 million**. The national economic burden of GDM can be reduced by interventions that reduce GDM.⁴ We believe that preventing GDM represents an opportunity to immediately improve the health and well-being of women and infants, potentially reduce the generational succession of the morbidity of GDM, and save millions of dollars incurred as a result of GDM. We also believe that targeting highest risk women will yield most benefit.

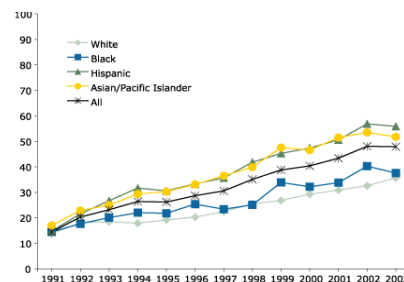


Figure 1. Rate of GDM in the U.S.¹

Potentially modifiable risk factors for GDM

Obesity is a significant risk factor for GDM. Unadjusted odds ratios (OR) of developing GDM of 2.14 (95% CI 1.82-2.53), 3.56 (3.05-4.21), and 8.56 (5.07-16.04) among overweight, obese, and severely obese compared with normal-weight pregnant women, respectively, have been reported.⁵ Furthermore, there is significant racial/ethnic disparity in GDM^{1,6}, with the largest relative increase in GDM occurring among African-American women. Primary prevention of obesity and management of weight gain during pregnancy would likely have a significant impact on GDM.

In a retrospective cohort study of 466 singleton pregnancies, we found that obese and overweight women were more likely than normal weight women (52% vs. 41% vs. 31%, $P < 0.05$) to have excessive gestational weight gain (GWG, a known risk factor for GDM), and that excessive GWG, independent of GDM, was associated with an increased risk for macrosomia in obese women (adj OR 2.5, 95%CI 1.1-6.3). Increasing GWG, particularly among women with GDM, was associated with a 20% increase in risk for a macrosomic infant, independent of maternal BMI.

Forty-50% of women with GDM will have GDM in a subsequent pregnancy,^{7,8} thus, development of GDM is a sentinel event in a woman's life that presents disease prevention opportunities. Primary prevention of obesity and management of weight gain during pregnancy would likely have a significant impact on GDM; however, **current macronutrient recommendations and dietary strategies for pregnant women have failed to reduce maternal obesity, excessive GWG, and prevalence of GDM**. This proposal will increase understanding of the biologic mechanisms of appetite signaling and satiety regulation as the first step toward developing dietary interventions to reduce GDM.

Interventions to prevent GDM

There is scanty level I evidence to support most aspects of the current nutritional prescription for preventing GDM. The American Diabetes Association recommends adequate calories to support fetal wellbeing while avoiding ketonemia.⁹ The recommended "routine" diet consists of 20% protein, 40% fat, and 40% of calories from complex carbohydrates with a low glycemic index because they are more nutrient dense and raise blood glucose less than simple sugars. However, there is no clear effect of this recommendation on pregnancy outcome. We believe that examining postprandial appetite signaling hormone and gut satiety peptide responses to varied macronutrient challenges is a valuable strategy for understanding short-comings in current dietary recommendations for preventing GWG and reducing GDM risk. We are specifically interested in differences in postprandial responses following low-glycemic meals that differ in protein content. Improved understanding of the biologic mechanisms of appetite and satiety in pregnant women would directly assist in planning future dietary interventions to reduce GDM risk.

Metformin has been associated with a 10-fold reduction in rate of GDM among women with polycystic ovarian syndrome.¹⁰ However, lifestyle interventions have provided mixed results: one study finding a 37% reduced risk for GDM in obese women who lost 10 or more pounds compared to women who did not lose weight,¹¹ but two randomized controlled trials found no differences compared to standard of care in rate of

GDM¹², maternal fasting blood glucose levels, insulin sensitivity, infant birth weight, or cost-effectiveness.¹³ Taken together, these results demonstrate the need for further understanding of the biologic mechanisms of appetite and satiety control to develop improved dietary strategies to promote healthy weight and reduce GDM.

Appetite signaling hormones and gut satiety peptides in pregnancy and GDM

Hunger, satiety, and glucose homeostasis depend on a complex feedback loop involving many hormones and other substances that interact with control centers in the brain. The gut participates in these pathways by secreting several hormones and peptides. **Table 1** lists the focused subset of these substances that will be studied in this proposal [ghrelin, peptide YY (PYY) and glucagon-like peptide-1 (GLP-1)]. Notably, ghrelin tends to be more responsive to carbohydrate and PYY and GLP-1 to protein.¹⁴ Ghrelin is a major signal for stimulating food intake and promoting positive energy balance. When administered peripherally or into the central nervous system, ghrelin stimulates secretion of growth hormone, increases food intake, and produces weight gain.^{15, 16} In rats, ghrelin and insulin responses to high fat/high energy diets promote weight gain in during pregnancy.^{17, 18} In human pregnancy, circulating levels of ghrelin peak at mid gestation, at the time of increasing maternal fat mass and insulin resistance. Regulation of maternal energy intake may be the prevailing effect of ghrelin in pregnancy and lactation.¹⁹ Ghrelin is suspected to be a diabetogenic factor and has been implicated in GDM.²⁰ Pregnant women who develop GDM have two-fold lower levels of ghrelin compared to women without GDM.²¹

Table 1. Appetite signaling hormones and gut peptides to be studied in this proposal		
Substance	Main Action	In pregnancy
Ghrelin	↑ appetite	↑ during preg ↓ in GDM
PYY	↓ appetite	Unknown
GLP-1	↑ insulin	↓ in GDM

PYY is a short polypeptide released by the ileum and colon in response to feeding. Animals overexpressing PYY have reduced body weight and food intake²² and protection against obesity.²³ PYY knock-out mice are predisposed to obesity and insulin resistance.²⁴ In humans, PYY reduces appetite. PYY concentration in the circulation increases after eating and decreases during fasting.²⁵ Protein consumption increases PYY levels, which reduces hunger and promotes weight loss²⁶, and blunted PYY secretion occurs in obese and diabetic individuals.²⁷ GLP-1 is another hormone also connected with glucose homeostasis. GLP-1 potentiates the insulin response to oral glucose, and its secretion is blunted in type 2 diabetes.^{28, 29} Fasting GLP-1 increases significantly from the second to third trimester of pregnancy, and levels are negatively correlated with infant birth weight. These data suggest that maternal GLP-1 regulation may be important in maternal metabolism and fetal growth.³⁰ During pregnancy, GLP-1 secretion is blunted following a glucose challenge among women who develop GDM.³⁰ Blunted GLP-1 secretion occurs in women with a previous history of GDM.³¹ GLP-1 levels appear to be inadequate in response to glucose levels among women with GDM.³²

In a series of studies in non-pregnant women, we found diminished postprandial ghrelin suppression in obese and non-obese women (**Figure 2**)³³; diminished postprandial ghrelin sensitivity to glycemic load (**Figure 3**)³⁴ and PYY release (**Figure 4**)³⁵ in black versus white women; and delayed postprandial GLP-1 release (**Figure 5**) in black vs. white women matched for age, BMI, and insulin sensitivity. Together, these data suggest that black women may be vulnerable to weight gain due to enhanced hunger signaling and diminished satiety signaling after food intake, coupled with a blunted sensitivity to dietary glycemic load manipulation. Notably, our data also indicate that ghrelin is suppressed to a

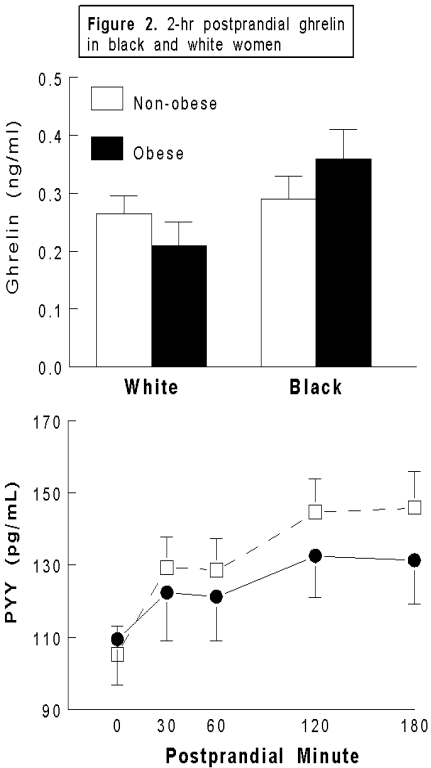


Figure 2. 2-hr postprandial ghrelin in black and white women

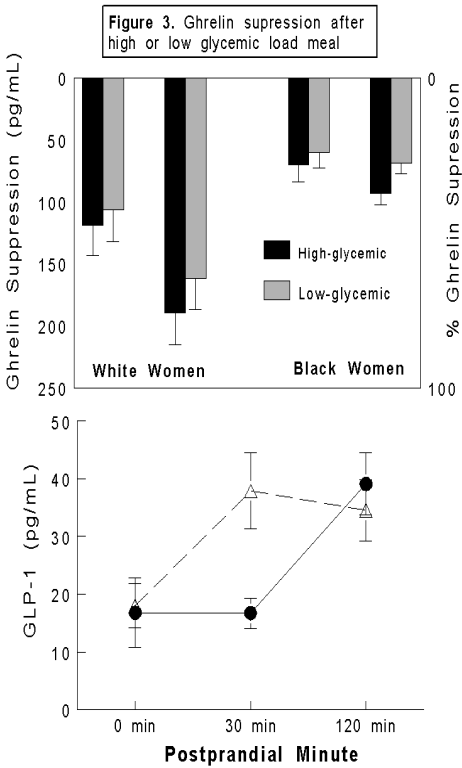


Figure 3. Ghrelin suppression after high or low glycemic load meal

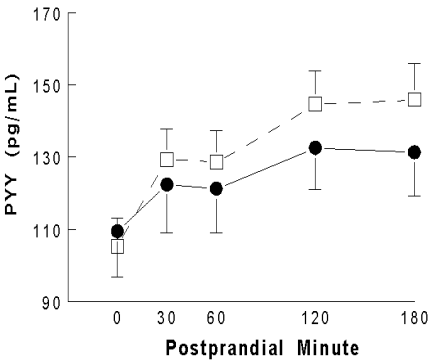


Figure 4. Postprandial PYY in obese black (circle) vs. white and non-obese black (square) women

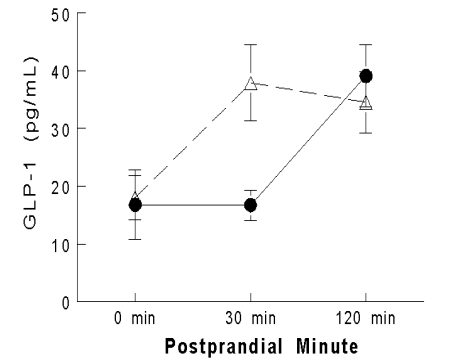


Figure 5. Postprandial GLP-1 levels in black (circle) and white (triangle) women.

lesser extent in white women after a low vs. a high glycemic load meal; thus, the satiating effects ascribed to low-glycemic meals are not likely mediated through changes in circulating ghrelin. Thus, meals designed to impact satiety through PYY may be more advantageous in promoting healthy weight.

In summary, these data suggest that ghrelin, PYY, and/or GLP-1 may be important in the pathogenesis of GDM. Dysregulated maternal appetite signaling hormone and gut satiety peptide responses may predispose to GDM; dietary modification may change maternal responses to favor healthy weight gain and glucose tolerance. **Understanding maternal appetite signaling hormone and gut satiety peptide responses to a full meal will inform development of specific dietary interventions to test in a future trial designed to reduce GDM risk.**

INNOVATION

We are committed to improving the health outcomes for women and children. Our **long-range goal** is to reduce the adverse effect of maternal GDM and obesity for both mother and child. While significant gains have been made in the treatment of GDM to improve maternal and infant outcomes, measures to prevent GDM, particularly among women at the highest risk, have fallen short. Our approach is innovative because we propose to study **dynamic** maternal postprandial appetite signaling hormone and gut satiety peptide levels, rather than a **static** examination at one time point or after fasting. This approach will result in data that will be used to develop specific dietary interventions to be tested in a future study. This proposal builds on current animal and human data regarding appetite signaling hormone and gut satiety peptide responses to address the knowledge gaps that exist and allow us to develop and test innovative strategies to prevent GDM.

APPROACH

We will conduct a randomized cross-over study of maternal appetite signaling hormone and gut satiety responses to a routine macronutrient meal versus higher protein meal. A detailed view of our study approach is shown in **Figure 6**. Annually, ~3100 women begin prenatal care at Women's Clinic: ~63% of women are parous (thus ~1950 eligible) and 6% have a prior history of medically treated GDM. In our previous clinical trials, ~50% of women were eligible and ~50% enrolled. Thirty women, 15 with a prior history of medically treated GDM and 15 without prior GDM will be enrolled between 20-22 weeks' gestation, frequency matched by maternal report of race. Women will be studied

Maternal serum and plasma, and subjective ratings of satiety and hunger, will be collected after overnight fast and then every 30 minutes after completion of the test meal for total of 3 hours. CTRC visits for different test meals will be 1-2 weeks apart.

Following completion of study procedures at the CTRC, women will continue with routine prenatal care as dictated by their primary care provider. Women will be asked to complete food-frequency questionnaires at enrollment and again at 32-34 weeks' gestation. Data on maternal GWG, inter-current pregnancy events (complications such as GDM, preeclampsia, etc), delivery events, infant birthweight, and infant hospital course, will be chart abstracted by research study staff.

Figure 6. Study Flow Diagram

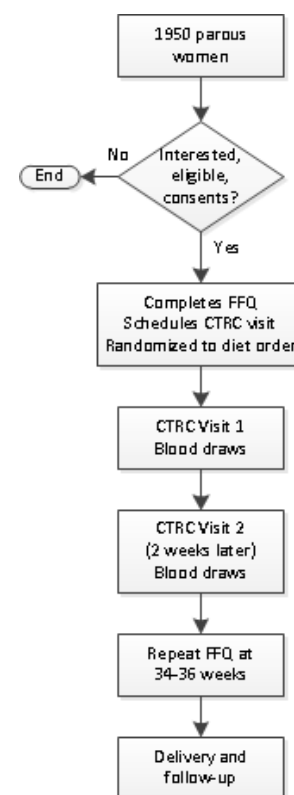


Table 2. Multidisciplinary research team		
		appetite regulation
	CTSA/co-I	Biostatistics
	CTSA/Registered Dietitian	Nutrition, meal planning

research proposal, including in-patient services, nutritional and dietary expertise, and specimen collection. In addition to leveraging the existing resources of the CTRC, **we**

have created a multidisciplinary team to ensure successful completion of this proposal (Table 2). To complement our study team, we have garnered the unreserved support (see letters of support) of the Senior Medical Director

at

, and the Project Director

all of whom are committed to

assisting with this proposal where needed to ensure successful completion.

Study Population and Procedures

30 pregnant women with a prior delivery (15 with history of GDM, 15 non-GDM) and BMI between 30-40 kg/m² at 20 - 22 weeks' gestation will be enrolled. Our rationale for this BMI and this gestational age is:

- Enrolling only obese women will limit confounding by maternal BMI and allow us to target women at high risk for GDM;
- Women in the 1st trimester often experience nausea, vomiting, and food aversions, which might affect their ability to tolerate a study diet;
- Women receiving care at _____ receive a 2nd trimester ultrasound to document viability and examine fetal anatomy; this prevents enrolling women with a miscarriage or fetal anomaly; and
- Women at risk for pre-gestational type 2 diabetes (previous GDM, BMI \geq 30 kg/m²) routinely undergo diabetic screening prior to 20 weeks; women with previously unrecognized pre-gestational type 2 diabetes that are identified in early pregnancy can then be excluded from enrollment.

Study entry criteria are shown in **Table 3**. Subjects will meet with study personnel to confirm eligibility and arrange for study visit. Maternal dietary information will be collected at baseline and at 32-34 weeks' gestation by the food frequency questionnaire. Maternal blood specimens will be collected at baseline and during study visit as described below and stored at the _____ Perinatal Research Laboratory until analysis.

Table 3. Inclusion/Exclusion Criteria	
Inclusion	Exclusion
One previous pregnancy – 15 w/prior GDM requiring medical treatment (oral or insulin) and 15 no prior GDM	Multiple gestation
Live, singleton fetus 20-22 weeks	Known or suspected fetal anomaly
No chronic metabolic or GI disease	Diabetes; Inflammatory Bowel or immune disorder; HIV infection; history of bariatric surgery, eating disorder
English speaking	Anemia (hemoglobin < 11.5 gm/dL)
BMI between 30-40 kg/m ²	

Enrollment will be conducted such that subjects in GDM and non-GDM groups are frequency matched by maternal self-report of race (white versus African-American), which will allow us to explore the potential interaction between maternal race and appetite signaling hormone and gut satiety peptide responses, as well as preclude one study group (prior GDM vs. no GDM) being predominantly one race and the other study group predominantly the other race. After screening and enrollment, women will be assigned dietary intervention (meal order) using computer-generated randomization; sealed envelopes containing sequential randomization numbers corresponding to study assignments will be opened after collecting all baseline data. All study procedures will be conducted _____. Women will receive routine prenatal care with dietary and weight gain recommendations, and undergo a standard obstetrical ultrasound, as prescribed by their primary prenatal care provider.

Enrollment, Consent, and Subject Tracking Process: Study staff will be on-site in the _____, where the _____ Women's Clinics are held. _____ Institutional Review Board (IRB) approval will be obtained with a waiver for consent to allow study staff to review clinic schedules and identify women who meet eligibility criteria. After check-in, study staff will approach potentially eligible women to inquire about interest in participation. At the time of enrollment, participating women will be assigned a unique study identifier. A master list linking the study identifier to the woman will be kept separately, on a password-protected computer that only the principal investigators or project manager can access. Specimens and data collection forms will be labeled with the unique study identifier. The master list will be destroyed per IRB guidelines.

Meal Composition: Glycemic index (GI) is a method of ranking foods based on the quality of the carbohydrate in the food as indicated by the foods' direct effect on blood glucose levels (higher GI = higher blood glucose). The glycemic load of a whole meal is calculated based on the carbohydrate content of the portion size consumed and GI of each food. Consumption of a low-glycemic load diet is purported to reduce appetite, and several studies have shown that subjective appetite suppression is sustained longer following consumption of a meal with a low- versus a high-glycemic load in obese individuals. The mechanisms linking low glycemic load with reduced appetite are not clear but may include alterations in appetitive hormones. Meals will be designed and prepared under the supervision of _____

_____ she will interview each subject at enrollment to identify food allergies and aversions. **Macronutrient composition for the routine meal will be 55% carbohydrate, 30% fat, 15% protein; for the higher protein**

meal, macronutrient composition will be 45% carbohydrate, 30% fat, 25% protein. Both meals will be low-glycemic (load = 30). A 1-2-wk washout period will separate the two meals.

Bioassays: Blood will be sampled at 30-min intervals for 3 hours after each meal. Blood samples will be stored at -70°C at the

Quantitative assays will be performed in batch analysis. Serum glucose will be measured using an Ortho Clinical Diagnostics Vitros 950 analyzer [sensitivity 20 mg/dL]. Insulin and active glucagon-like peptide 1, peptide YY (PYY3-36), and ghrelin will be measured using commercially available radioimmunoassay kits and following the manufacturer's instructions for sample collection. Dr.

has experience using these kits and publishing data derived from them.

Maternal dietary assessment: We will measure maternal dietary intake at enrollment and again at 32-34 weeks, using a modified version of the National Cancer Institute-Block Food Frequency Questionnaire,³⁶ which has been validated in a number of studies in a variety of populations, including pregnant women in

Maternal weight assessment: We will measure maternal weight and height by previously published methods.

GWG will be determined using Institute of Medicine (IOM) data points: maternal report of pre-gravid weight will be subtracted from the last reported weight prior to delivery. Excessive GWG is defined by 2009 IOM guidelines (**Table 4**).

Table 4. 2009 IOM Guidelines for GWG	
Pre-pregnancy BMI kg/m ²	Total GWG
Underweight < 18.5 kg/m ²	28-40 lbs
Normal weight 18.5-24.9 kg/m ²	25-35 lbs
Overweight 25-29.9 kg/m ²	15-25 lbs
Obese > 30 kg/m ²	11-20 lbs

Pregnancy Outcome Data: Gestational age at delivery, infant birthweight, and infant gender will be recorded at delivery. Preterm delivery will be defined as delivery at < 37 weeks' gestation, and will be further characterized as spontaneous or medically indicated. Preeclampsia will be defined as new onset hypertension (blood pressure > 140/90 on two occasions, 6 hours apart) and proteinuria (urine protein/creatinine ratio > 0.15 or > 300 mg/dL protein on a 24-hour urine collection). Large for gestational age is defined as infant birthweight > 90th percentile for gestational age, and GDM as a positive 3 hour 100 gm glucose tolerance test³⁸ requiring either an oral hypoglycemic agent or insulin to achieve glycemic control.

Incentives: Women will receive parking vouchers, and \$50 per CTSC per visit. Women will receive \$5 for each FFQ completed, for a total maximum incentive to be \$110.

Statistical Analysis

All statistical analysis plans have been developed in collaboration with , Biostatistician. Prior to statistical analyses, we will calculate Areas Under the Curve (AUC) for PYY, ghrelin, and GLP-1, as well as insulin and glucose, using the trapezoidal method.

Specific Aim 1) To measure appetite signaling hormone and gut satiety peptide levels following mixed macronutrient meals among women with and without prior history of GDM;

Specific Aim 2) To quantify maternal appetite signaling hormone and gut satiety peptide responses following a routine low-glycemic meal vs. a higher protein low-glycemic meal

To accomplish aims 1 and 2, we will use linear mixed models with the values as the outcomes, with separate models for each hormone and peptide. Primarily, each model will contain fixed effects for group (with or without prior history of GDM), meal (routine macronutrient meal versus higher protein meal), the interaction of group and meal, period (random order of meals), baseline BMI, and race. For subsequent exploratory analyses, we will also include interactions with race. Each model will also contain random intercepts for each woman to account for correlation between repeated measurements. We will use appropriately specified contrasts for tests at the two-sided 0.05 significance level for each aim.

Specific Aim 3) To measure association between fasting and postprandial appetite signaling hormone and gut satiety peptide responses and pregnancy outcomes (maternal GWG, infant birthweight, presence of GDM).

To achieve aim 3, we will use either linear regression models (with GWG or infant birthweight as the outcome) or logistic regression models (with GDM as the outcome) and the postprandial responses to each

meal as the independent variables. Due to sample size, we will fit separate models for each hormone and peptide. These models will control for baseline BMI and race.

Sample size considerations: We calculated power for Specific Aims 1 and 2 using a standard approach for mixed models.³⁹ Briefly, we used data from our previous studies^{34, 35} to estimate relevant variance/covariance parameters for PYY and ghrelin as well as the expected AUC values for obese women following a whole food meal. We used the estimated expected values to create exemplary datasets to which we applied a variety of feasible effect sizes, and we used these exemplary datasets along with the estimated variance/covariance parameters to calculate power. We estimated the mean PYY AUC will be ~400 pg-hr/ml, with a standard deviation of ~84 pg-hr/ml and a within-woman correlation of ~0.6. Under these assumptions, enrolling 30 women will provide at least 80% power to detect a mean difference of 40 pg-hr/ml (i.e., ~ a 10% difference) between meals (Aim 2, a within-woman comparison) and at least 80% power to detect a mean difference of 80 pg-hr/ml (i.e., ~ a 20% difference) between women with and without prior history of GDM (Aim 1, a between-group comparison) using two-sided alpha = 0.05. For ghrelin, we estimated that the mean AUC will be ~1700 pmol-hr/L, with a standard deviation of ~525 pmol-hr/L and within-woman correlation of ~0.93. Under these assumptions, the respective tests would provide at least 80% power to detect mean differences of 110 pmol-hr/L (i.e., a 6% difference) between meals and 540 pmol-hr/L (i.e., a 32% difference) between groups.

Potential Pitfalls and Alternative Strategies.

Subject enrollment and retention to complete all study procedures is a challenge for any clinical study. Our previous experience with clinical trials, some of which were very involved and invasive, demonstrates our ability to recruit and retain subjects. In the Maternal Fetal Medicine Units Network study of GDM, we were able to complete follow up on 92% of subjects,⁴⁰ so we feel that incomplete data is unlikely in this study. However, in the event that a subject withdraws prior to completion of both study visits she will be replaced to prevent missing data.

It is possible that PYY responses are different between the routine and the higher protein meals, but to a lesser extent than can be tested by our study. Even if we do not demonstrate a statistically significant difference in PYY, our study will generate informative data that will add to the body of knowledge of appetite signaling during pregnancy, particularly among a high-risk group of women.

A high protein diet increases urinary calcium excretion with potential risk for nephrolithiasis and bone loss.⁴¹ While the risk for bone loss is controversial, we believe that a single high protein meal is unlikely to adversely affect calcium homeostasis or bone metabolism. Further studies on high protein diet in pregnancy will need to monitor urinary calcium excretion and bone metabolism.

Appetite regulation is complex and involves many interacting components, including a number of signaling mechanisms. Many hormones and peptides other than ghrelin, PYY, and GLP-1 may be important in GDM risk during pregnancy. We will store maternal specimens for future use to measure other appetite regulatory pathways (e.g. leptin, obestatin,).

Project Timeline and Benchmarks (B) for Success. The proposed study, including team meetings to discuss study progress, will be accomplished in a 2-yr period according to the time-line below. We anticipate enrolling ~3 women with prior GDM per month for 5 months to achieve our desired sample size; we will enroll women with no prior history of GDM concurrently.

	Year 1								Year 2								B1 Final enrollment/study visits B2 Final delivery data collected B3 Specific analysis completed B4 Data analysis complete *Study team meeting
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	
Study Startup	*																
Screen/Enroll			*														
CTRC Visits								B1									
Delivery FU							*		B2								
Specimen Analysis										B3							
Data Check											*						
Data Analysis																B4	
Final Report																*	

PROTECTION OF HUMAN SUBJECTS

Risks to Human Subjects

a. Human Subjects Involvement, Characteristics, and Design

Study personnel will screen prenatal records under a limited waiver of HIPAA granted by the [redacted] to determine if a patient meets eligibility requirements. Women are eligible if ≥ 18 years of age, have a prior history of medically treated gestational diabetes (oral hypoglycemic agents such as metformin or glyburide, or insulin) and are pregnant with a singleton fetus 20-22 weeks with no known anomalies. If eligible, study personnel will approach medical provider to determine appropriateness of patient to serve as a study subject (i.e., to avoid inadvertently approaching a woman who has experienced a fetal death, but it is not recorded yet in the medical record). If appropriate, study personnel will invite the patient to serve as a study subject. We will enroll 20 women over 4 months.

Study personnel will describe the study in detail and review the study protocol with the patient. Women agreeing to participate will sign a consent form; one copy will be placed in their medical record, and a copy will be given to the patient for her records. Enrolled subjects will be scheduled for a CTRC study visit, and medical review will be done to collect research information. All subjects will complete a food frequency questionnaire (Diet History Questionnaire (DHQ): a semi-quantitative FFQ which uses an embedded question approach developed by the National Cancer Institute; web-based version available free of cost.

b. Sources of Materials

Study personnel will collect the following from enrolled subjects:

1. Medical history and overall health information (medical chart abstraction).
2. Blood collected at 2 study visits at
3. Maternal weight at baseline.
4. Delivery and infant data (medical chart abstraction).

All information and specimens that are collected will be used for study purposes only. At enrollment, patients are assigned a unique study number, which is then used to identify all information and specimens collected as part of the study. Medical, prenatal, and delivery data will be recorded on data collection forms and then entered into the study database, using an ACCESS database specifically created for this study. All specimens collected will be labeled with preprinted barcoded labels with a unique study number assigned to the patient. The list with the linkage of unique study number to a specific patient is kept in a locked file on a password-protected computer that only the data manager has access.

c. Potential Risks

There is limited risk from participation in this study. Women may find the meals provided to be unappealing. There is also risk for breach of confidentiality, which is inherent to any clinical research project.

Adequacy of protection against risks

a. Recruitment and Informed Consent

Women who agree to participate will have the study explained to them orally by study personnel. Written consent will be obtained and a signed copy of the consent form will be maintained in the patient record, as part of the study record, and given to the patient. Enrolled subjects can decline to participate or cease participation at any time with no adverse consequences.

Consent will be sought and obtained by trained research study personnel. The study will be explained in detail, and all questions will be answered. Consent will be documented in writing. A limited waiver of HIPAA will be obtained to allow study staff to review clinical logs to determine if potentially eligible subjects are available.

b. Protections Against Risk

Subject may discontinue study medication at any time. All assurances are made to keep medical data confidential. Data collected as part of this study is collected on study forms that are identified with a unique study number assigned at enrollment. No patient identifiers will be on study data collection forms. The link between specific subjects and unique study numbers is kept separately, on a password-protected computer that only the data manager can access. There is a very low-likelihood ($< 1\%$) of breach of privacy or confidentiality.

Potential benefits of the proposed research to human subjects and others

There is no direct benefit to the patient for study participation. The benefit is the knowledge to be gained. The risks are reasonable in relation to the potential knowledge to be gained.

Importance of the knowledge to be gained

Gestational diabetes is a critical public health issue with increasing frequency that can adversely long term maternal and infant health. Current dietary recommendations fail to reduce recurrent GDM risk. The results generated by this proposal will serve as pilot data for an application for extramural funding for a randomized trial of different dietary strategies to reduce adverse pregnancy outcomes to improve maternal and infant health.

INCLUSION OF WOMEN AND MINORITIES

The target population for this proposal is pregnant women with previous GDM. The racial/ethnic distribution of the prospective study population will reflect the racial/ethnic distribution of the women who receive care at _____, which is 40% white, 18% black, and 38% Hispanic. All adult participants are female; infant participants will be 51% male and 49% female which is the typical gender representation of births at _____ hospitals.

Targeted/Planned Enrollment Table

This report format should NOT be used for data collection from study participants.

Study Title: **Appetite Hormone and Gut Peptide Responses in Pregnancy**

Total Planned Enrollment: 30 mothers

TARGETED/PLANNED ENROLLMENT: Number of Subjects			
Ethnic Category	Sex/Gender		
	Females	Males	Total
Hispanic or Latino	3		3
Not Hispanic or Latino	27		27
Ethnic Category: Total of All Subjects*	30		30
Racial Categories			
American Indian/Alaska Native	0		
Asian	0		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	15		15
White	15		15
Racial Categories: Total of All Subjects*	30		30

* The "Ethnic Category: Total of All Subjects" must be equal to the "Racial Categories: Total of All Subjects."

INCLUSION OF CHILDREN

Mothers less than 18 years of age are excluded from participation. Individuals under the age of 18 years are considered minors at the

requires that parental consent be obtained for research involving minor children. Women will be recruited at the time of admission to Labor and Delivery for delivery of their infant, and these women often do not have their parents with them, which makes obtaining parental consent impossible. As such, women under the age of 18 years at the time of enrollment into the study will be excluded from the research protocol. Neonatal information collected as part of this study will be determined from the mother's medical record.

References

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Principal Investigator/Program Director (Last, first, middle):

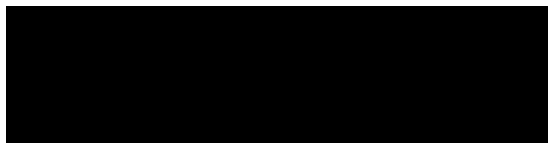
January 21, 2013

Dear

I am pleased to write this ***unreserved letter of support*** for your proposal to study appetite signaling and gut peptide hormone responses to a full meal among pregnant women at risk for gestational diabetes. The prevalence of gestational diabetes is increasing, particularly among African-American women, and our current prevention strategies are falling short.

As Senior Medical Director of Ambulatory Services, I am fully supportive of your role as Principal Investigator for this proposal and will facilitate recruitment to ensure success of the project. Congratulations on embarking on the work necessary to improve the health of women and children. I am confident that the results obtained from this proposal will lead to important information to be used to plan further studies.

Sincerely,

A large black rectangular box redacting the signature and name of the Principal Investigator.

Principal Investigator/Program Director (Last, first, middle):

Checklist

OMB Number:

1. Application Type:

From SF 424 (R&R) Cover Page. The responses provided on the R&R cover page are repeated here for your reference, as you answer the questions that are specific to the

* Type of Application:

☒ New ☐ Resubmission ☐ Renewal ☐ Continuation ☐ Revision

Federal Identifier:

2. Change of Investigator / Change of Institution Questions

☐ Change of principal investigator / program director

Name of former principal investigator / program director:

Prefix:

* First Name:

Middle Name:

* Last Name:

Suffix:

☐ Change of Grantee Institution

* Name of former institution:

3. Inventions and Patents (For renewal applications only)

* Inventions and Patents: Yes ☐ No ☐

If the answer is "Yes" then please answer the following:

* Previously Reported: Yes ☐ No ☐

4. * Program Income

Is program income anticipated during the periods for which the grant support is requested?

☐ Yes ☒ No

If you checked "yes" above (indicating that program income is anticipated), then use the format below to reflect the amount and source(s). Otherwise, leave this section blank.

*Budget Period *Anticipated Amount (\$)

*Source(s)

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5. * Disclosure Permission Statement

If this application does not result in an award, is the Government permitted to disclose the title of your proposed project, and the name, address, telephone number and e-mail address of the official signing for the applicant organization, to organizations that may be interested in contacting you for further information (e.g., possible collaborations, investment)?

☒ Yes ☐ No